



A review of best evidenced-based enteral and parenteral nutrition support practices for preterm infants born <1,500 grams

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Abstract: Nutrition monitoring must remain a priority for very low birth weight infants who are at high risk for nutritional deficiencies and growth failure. Research demonstrates that as many as 50% of North American infants experience extrauterine growth failure, primarily attributable to inadequate nutrition delivery. Consequently, the purpose of this review is to identify the best enteral and parenteral nutrition management practices for preterm infants born <1,500 grams. Nutrition recommendations set forth for preterm infants by leading references were reviewed and compared. Infant nutrition and growth studies identified by extensive literature review were also assessed in comparison to current recommendations, neonatal clinical experience, and gaps within clinical practice. Modern literature demonstrates that more aggressive parenteral nutrition provision, early enteral feeding initiation, more rapid enteral feeding advancement, and early human milk fortification are well tolerated and promote improved nutrition, growth, and clinical outcomes. This review identifies clinically feasible and evidenced-based enteral and parenteral nutrition support practices that promote best outcomes for very low birth weight infants.

Keywords: Enteral nutrition; parenteral nutrition; growth; very low birth weight; <1,500 grams; preterm infant

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Introduction

It remains well-recognized that adequate growth is critical for every preterm infant, and most specifically for those born very low birth weight at <1,500 grams. These infants have exceedingly high nutrient needs, so providing adequate nutrition is necessary to meet full potential for growth and neurological outcomes. Despite this knowledge, recent data reports that 50% of North American infants born <1,500 grams are still experiencing postnatal growth failure with discharge weights plotting below the 10th% on their respective growth charts (1). Furthermore, it is reported that up to 27.5% of these same infants are being discharged with severe growth failure, defined as discharge

weights plotting less than the third percentile for age (1). Unaggressive, dated nutrition practices contribute to calorie and protein deficits, all resulting in subsequent poor growth. These include but are not limited to a low optimization of parenteral nutrition (PN), delay in enteral feeding advancement, and delay in human milk fortification. Poor nutrition management can lead to osteopenia, cholestasis, chronic lung disease, and a multitude of other issues that further deplete nutrient stores and affect growth (2). Nutrition practices vary significantly among neonatal units, but achieving adequate growth must remain a common and consistent priority. Nutrition management must be regarded as a true medical therapy. While therapies like respiratory support remain an immediate forefront priority,

it is the persistent adequate nutrition support that will influence these long-term adjunctive therapy requirements. Furthermore, it is important to recognize that improved growth has been associated with a lower risk of cerebral palsy and developmental delay in the smallest of infants, both of which affect lifelong outcomes (3). Therefore, the purpose of this literature review is to summarize the most optimal and current evidenced-based nutrition practices for preterm infants, specifically those born <1,500 grams. In addition, gaps within current available recommendations for these infants are identified and best practice strategies are discussed to adapt into clinical practice.

Review of the literature

The following details recommendations and optimal practices for enhancing nutrition delivery to very low birth weight preterm infants.

Parenteral nutrition

Indications

Outside of gastrointestinal or perfusion concerns, the American Academy of Nutrition and Dietetics (AND) primarily recommends the use of PN in infants born <30–32 weeks gestational age or those weighing <1,500 grams (4). These infants have the highest metabolic requirements for growth. Infants receiving early and adequate PN regain birth weight more quickly and experience improved weight gain and head growth (5,6). In addition, when administered PN these infants accrue fewer deficits for energy and protein in the first week of life, which influences later growth outcomes (7). Studies have further demonstrated the importance of cumulative intake in the first week of life as increased provision, specifically of protein, influences neurodevelopmental scores at 18 months of age (8).

Custom PN

Providing custom PN offers advantages over premixed solutions, particularly to the high-risk infant as the nutrition regimen is directly tailored to meet their individual needs.

Intralipids

Intralipids are an essential component of PN, not only to provide adequate energy, but also to prevent early essential fatty acid deficiency in the extremely low birth weight infant. Maximum hourly infusion rates are standardly recommended at 0.12–0.15 grams/kg/hour (will provide

2.9–3.6 grams of fat/kg/day over 24-hour period) (4). Rates of 0.08 grams/kg/hour (1.9 grams/kg/day over 24-hour period) can still be tolerated if lipid intolerance presents during periods of acute stress or sepsis (4). AND recommends starting lipids at 0.5–1.0 gram/kg/day within the first 24 hours of life and advancing by 0.5–1.0 gram/kg/day daily toward goal of up to 3 grams/kg/day with a maximum safe dose being 4.0 grams/kg/day (4). However, a study by Drenckpohl *et al.* assessed starting lipids at 0.5 grams/kg/day in the control group *vs.* 2 grams/kg/day in the study group for infants born 750–1,500 grams (9). They found that the higher dose was well tolerated and these infants achieved higher daily energy intakes during the first week of life compared to the control group. Study infants also had less retinopathy of prematurity and fewer were discharged at <10th% for weight (9). Not only does higher early dosing contribute to improved energy provision, but has been subsequently correlated to improved weight gain and a lower incidence of retinopathy of prematurity (10). Historically, intralipid dosing may be delayed or advanced slowly based on mixed reports about its association with outcomes like chronic lung disease, pulmonary hypertension, or sepsis (4). However in a recent review by Salama *et al.* regarding intralipid use in preterm infants, they summarized that the benefits to early and higher dosing far exceeded any potential risks (11). They also question slow advancement of intralipid dosing, as several studies demonstrate appropriate tolerance in term and preterm newborns when starting lipids at a minimum of 2 grams/kg/day (11). They also report that slow advancements do not improve clearance rates (11).

Clinically, hypertriglyceridemia may develop in the smallest of infants, coinciding most frequently when significant hyperglycemia persists. Triglyceride levels may be monitored in this instance. Maximum allowance of triglyceride levels are not well defined and remain variable by unit. In the Salama *et al.* review, 250–300 mg/dL may be empirically selected with 400 mg/dL being the potential level of lipid saturation (11). Utilizing higher tolerable levels allows more leverage for continuing higher lipid dosing and providing improved energy provision. There are minimal available recommendations for lipid management when hypertriglyceridemia is present. It should be important to recognize that reducing lipid dosing will subsequently decrease calorie provision, so ideally intralipids would not be decreased by more than necessary. Clinical experience suggests lipid levels clear quickly in very low birth weight infants, so eliminating lipids completely will only further contribute to nutrition deficits. AND recommends

decreasing lipid dosing by 0.5–1.0 grams/kg/day in instances of high triglycerides (which they set as >200 mg/dL) (4).

Intralipid type, dose, and timing can be altered in instances when substantial enteral feedings are unfeasible or cholestasis progresses. AND suggests cyclic administration of PN to prevent conjugated hyperbilirubinemia, though additional details on this are not available (12). In instances of conjugated hyperbilirubinemia, lipids may be cycled daily over 12 hours to allow liver clearance. Total daily lipid dose may also be decreased to no less than an average of 0.5–1.0 gram/kg/day to prevent essential fatty acid deficiency (4). This nonetheless remains a less frequent occurrence in a population of very low birth weight infants who receive early initiation and advancement of full enteral feedings. In the event of cholestasis or anticipated prolonged PN, clinical decisions regarding type of intralipid use must be considered. Available alternative options include Omegaven or SMOFlipid, which contain a higher amount of Omega 3 fatty acids in comparison to Omega 6 fatty acids (12–14).

Protein

Recommended parenteral protein for preterm infants consists of a starting dose of 2–3 grams/kg/day, a transitional dose of 3.5–4.0 grams/kg/day, with a maximum safe dose of 4.0 grams/kg/day (4). AND reports that starting amino acid infusion within the first 24 hours of life promotes positive nitrogen balance, with up to 3.0 grams/kg/day being a safe starting dose (4). Long-term exposure to high doses have not demonstrated a clear benefit based on currently-available literature. Additionally, outcomes of parenteral protein provisions at >4.0 grams/kg/day have not been extensively studied. However of interest, Loui *et al.* aimed for goal of 4.5 grams (achieved target of 4.3 grams/kg/day) of parenteral protein/kg/day for infants <1,000 grams and 4.0 grams/kg/day for infants 1,000–1,500 grams (15). This was followed by 4.5–5.0 grams protein/kg/day when full enteral feedings were achieved. This resulted in median weight gain from day 8–35 of 17.6 grams/kg/day and appropriate head growth (15). Higher parenteral protein doses have also been associated with improved early glucose control in very low birth weight infants receiving equal non-protein energy (16). Most important is that early adequate protein is associated with improved neurodevelopmental scores in later life (8).

Initiating early protein provision should not be hindered by fears of metabolic intolerance, as there remains little evidence demonstrating severe metabolic disturbances from this practice (17). A further review of current practices reports that current parenteral recommendations

may invoke adverse effects of ionic balances and certain electrolytes like phosphorus (18). However, they conclude that clinicians should monitor for these changes to prevent or correct as needed in order to “potentiate the positive effects of optimal PN on long-term neurocognitive development in neonates” (18). Protein can also be initiated at levels as high as 3.5 grams/kg/day without significant side effects (19). Advancement to higher end doses of 4.0 grams/kg/day may be done stepwise, but this is based on personal preference over available evidence (19). Metabolic acidosis and elevated blood urea nitrogen levels within the first week of life may coexist with recommended protein provisions, but this is likely multifactorial and also attributed to decreasing gestational age and more immature metabolic processes. There is currently no strong evidence to adjust parenteral protein provisions based on blood urea nitrogen levels alone when creatinine levels and hydration status are appropriate.

Dextrose

Dextrose infusion from PN will vary dependent on blood glucose levels, estimated energy needs, and enteral feeding. AND recommends beginning glucose infusion rates between 4–6 mg/kg/minute (4). The goal range is between 5–15 with maximum of 18 mg/kg/day (4). Rate advancement is not well defined, especially as each infant may tolerate dextrose at varying levels. The goal is to optimize energy intake, but also prevent significant hyperglycemia, which can be a common occurrence in the smallest of infants (20). Insulin use is a treatment option to provide a balance between the two, however precise administration remains a challenge. AND recommends considering insulin use when blood glucoses are elevated (>180 mg/dL) or when the glucose infusion rate must be restricted to less than 6 mg/kg/minute to promote euglycemia (4). Overall, consensus recommendations for hyperglycemia management in low birth weight infants currently remain inconclusive (21).

Clinical experience demonstrates that glucose infusion rate advancement of roughly 1.5–2.0 is tolerated in larger, more stable infants. Advancement is more cautious in infants <750 grams or those born <28 weeks if blood glucose levels remain elevated. However, the benefit of early and more aggressive advancement of enteral feedings is that infants receive more energy from enteral feedings, which limits the need for high provision of parenteral dextrose.

Total parenteral calories needed to meet basal needs in preterm infants range from 46–55 calories/kg/day (4). Goal parenteral ranges needed to promote growth are 90–115 calories/kg/day (4).

Enteral nutrition

The following details optimal enteral nutrition recommendations and best practices to enhance nutrient delivery to very low birth weight infants.

Initiation and advancement of enteral feedings

Initiation of enteral feedings may be delayed in very preterm or low birth weight infants due to concern for intolerance and necrotizing enterocolitis (NEC). There is limited research to support this practice as low enteral volumes are well tolerated and late introduction of feedings does not further reduce NEC risk (22). In a Cochrane analysis of infants <1,500 grams, including a subset of growth restricted infants, no discernible benefit was found to initiating enteral feedings after day of life four (23). Delaying feedings only contributes to a prolonged time to achieve full enteral feedings while requiring longer PN use (24). Trophic feedings theoretically promote intestinal maturation in the smallest infants, but time of treatment to allow maximum benefit has not been well defined. One point to consider is that infants swallow amniotic fluid in utero, so the gastrointestinal track is in use and is receiving various nutrients (25). As a result, early initiation of enteral feedings following birth should theoretically allow for intestinal continuity, prevent villous atrophy, and therefore limit the need for a lengthy trophic feeding period. A recent study of infants born 23–28 weeks gestational age (N=192) demonstrated a shorter trophic feed duration of median 2 days (IQR 2–3 days) *vs.* 6 days (IQR 5–7 days) did not increase risk of NEC or spontaneous intestinal perforation (26). After feeding initiation, a Cochrane review from 2014 suggests that enteral feedings can be safely advanced by 30–35 mL/kg/day in very low birth weight infants without increased risk for NEC (27). An updated review on this indicates up to 40 mL/kg/day advancement is tolerable, most specifically among infants between 1,000–1,500 grams (24). An advancement of 30 mL/kg can still be utilized in infants weighing as little as 750 grams (28). Limited consensus data is available for infants <750 grams. Data by Viswanathan *et al.* recently reported that a slow standardized enteral feeding protocol reduced the incidence of NEC in infants <750 grams (29). Infants were withheld enteral feedings for the first 10–14 days of life and reportedly advanced at <10 mL/kg/day (29). NEC was reduced (16.2 decreased to 1.1%), however noted were higher alkaline phosphatase levels, high incidence of cholestasis, increased days receiving parenteral nutrition, and increased days with a central line (29). Controversy of

this strategy may exist, as this significantly delays enteral initiation, may result in early-life gut atrophy, and delay immunity benefits received from mother's own milk provision. It also prolongs the need for supplemental PN and may invoke further nutritional deficits if parenteral nutrient shortages exist (30). Furthermore, this may not be the most optimal nutrition strategy for units experiencing lower incidence rates of NEC while simultaneously reporting success in considerably faster initiation and advanced of enteral feedings for extremely low birth weight infants (31).

One hindrance to early achievement of full enteral feedings is providing indomethacin or ibuprofen in early life to promote closure of a patent ductus arteriosus. Enteral feedings are often minimized or held during treatment secondary to concern for bowel perforation, yet trophic feedings are still be feasible. Clyman *et al.* demonstrated that 15 mL/kg continued trophic feedings in infants <1250 grams being treated with either drug achieved full enteral feedings more quickly compared to infants who had their feedings held during treatment (32). There were also no increases in NEC or bowel perforations (32). Infants in Clyman's study had never achieved >60 mL/kg/day enteral feedings, received human milk fortification, or had received a preterm formula at >20 calories/ounce (32). However, a recent article Louis *et al.* also demonstrated that infants born <1,500 grams can receive >60 mL/kg/day of enteral feedings during indomethacin treatment without an increased risk of NEC (33).

Human milk fortification

The use of human milk fortifiers (HMF) is an essential therapy for the human milk fed preterm infant. Fortification of maternal breast milk (MBM) or donor human milk should begin in the early stages of enteral volume advancement and as PN is weaned. An optimal goal is to achieve full fortification with HMF and supplemental protein as needed prior to discontinuation of PN in an effort to limit days of suboptimal nutrient intake, as Miller *et al.* exemplified the transition from full parenteral to full enteral nutrition as a determinant of later growth failure (34). A partial reason for this was the lower protein provision with decreasing supplemental PN use (34). With faster enteral feeding advancement, less nutrition is received from PN. Therefore, human milk fortification should be initiated earlier, with past studies even demonstrating tolerance of fortification at 40 mL/kg/day or at first feeding initiation (35–37).

Strong indications for use of HMF include infants

<34 weeks, infants weighing <1,500 grams, infants who received >2 weeks of total parenteral nutrition, or infants >1,500 grams who are fluid restricted or have experienced poor growth (38). HMF may be used beyond these criteria to optimize nutrition and growth. Recommendations from two leading North American HMF manufacturers state their products can be used until an infant is either receiving 20 vials per day of HMF [~600 mL prepared 24 calorie/oz (ounce) milk] (39) or until reaching a weight of 3.6 kg (40). Therefore, infants born <1,500 grams may be able to receive human milk fortifiers for most of their NICU hospitalization to keep nutrient provision optimized.

Providing adequate early energy is essential to prevent nutritional deficits and early growth failure. Recommended calorie goals for infants <1,000 grams range between 130–150 calories/kg/day, with a goal of 110–130 calories/kg/day for infants 1,000–1,500 grams (41). Provision of 120 calories/kg/day is a common starting goal for infants <1,500 grams having just achieved full enteral feedings. This should theoretically support adequate early growth and further adjustments can be made as needed based on an infant's growth pattern.

Estimated enteral protein needs based on size and gestational age varies in the literature. The American Academy of Pediatrics recommends a range of 3.8–4.4 grams/kg/day for infants <1,000 grams, followed by a recommended dose of 3.4–4.2 grams/kg/day for infants 1,000–1,500 grams (38,41). Wagner *et al.* summarized recommended enteral protein needs from varying sources (42). Most notable from this summarization was the highest end range for recommended protein for infants <1,200 grams or <30 weeks gestational age across all references ranging from 4.0–4.8 grams/kg/day with the highest end range for infants up to 36 weeks gestational age across all references being 3.0–4.2 grams/kg/day (42). The safe maximum upper limit was reported as 4.9 grams/kg/day (42). One consideration for higher-end of recommended protein provision is that rapid growth and brain development are occurring during preterm gestational ages. Therefore, the potential risks of providing inadequate protein may be greater than those of providing more than minimally needed. As growth during prematurity and early infancy can affect life-long outcomes (3), it is important to prevent under-nutrition and subsequent growth failure.

The protein content of human milk remains variable. Firstly, maternal milk contains higher protein during the first weeks following preterm delivery (43,44), a common reference of 14 grams per liter (45). Mature human milk is reported to contain approximately 10.5 grams per liter (45). Donor human milk often yields a considerably lower

protein content due to the later lactation stages of donor mothers and required heat pasteurization. Observation in clinical practice demonstrates that most donor milk received contains 8–9 grams/Liter. Monitoring of human milk type must be considered in order to appropriately adjust supplemental PN or milk fortification to achieve protein goals and to not over or underestimate nutrition delivery. While human milk fortifiers substantially increase provided protein, not all versions will achieve goal ranges. As a result, protein modulators remain an essential component of appropriate human milk fortification.

Protein and calorie requirements for infants may vary with increasing maturational age dependent on previous growth, labs, and clinical course. There are guidelines and suggestions based on gestational age and weight (42), however clinical judgment is also necessary for individualized care. One consideration is to ensure adequate energy and protein delivery during an infant's transition from gavage feedings to feeding at breast. Direct breastfeeding will limit intake of fortified milk in infants receiving a primarily human milk diet. One way to assess nutrient intake from breastfeeding is to implement pre and post weights (46). These pre and post weights can also aid in determining the appropriate gavage supplementation if full feedings are unable to be taken at breast. Continuing human milk fortification and protein modulators in fortified pumped MBM will optimize total daily energy, protein, and micronutrient intake if a portion of their total feeding volume is unfortified milk from breastfeeding attempts. Additionally, the protein content of MBM will have decreased over the period of several weeks or months that a mother has provided milk for her very or extremely preterm infant. It may be considered best to optimize protein in the interim if they will eventually transition to less substantial human milk fortification at discharge. Furthermore, continued fortification will ideally aid with weight gain, head growth, bone mineralization, and accrual of lean body mass.

Human milk fortifiers made with bovine milk protein, either intact or extensively hydrolyzed, are the most widely available options in North America for the human milk fed preterm infants (39,47,48). There also remains a human-milk based human milk fortifier available for use (49). If using the bovine milk protein-based fortifier, the extensively hydrolyzed version may be used for intolerance and provides substantially improved nutrition when compared to using an elemental or semi-elemental infant formula powder to fortify milk, given its higher content of essential protein, vitamins, and minerals (47). The primary consideration

of this practice, however, is the questionability of altered nitrogen retention and growth in infants receiving most of their protein supplementation in hydrolyzed form (50). As suggested in a review by Szajewska, total hydrolyzed protein provision can be increased by at least 10% to account for these differences (50). This can be achieved by the addition of an extensively hydrolyzed liquid protein modular (51), or else an amino acid protein modular in instances of severe intolerance (52).

Supplemental feedings beyond maternal milk

Donor human milk is one option as a supplement to MBM, but the advantages and disadvantages of using donor milk as a supplement must be weighed. The most prominent considerations include risk of NEC, potential growth alterations, and overall developmental outcomes when compared to using preterm infant formula (53,54).

Eligibility requirements vary from one unit to another. Donor milk may be labeled at caloric densities >20 calories/ounce based on testing (i.e., 22 or 24 calories/ounce), but this difference is due to higher fat content so human milk fortifiers are still added to provide an additional 4 calories/ounce. While this mathematically achieves higher than the targeted 24 calorie/ounce feeding, preterm infants meeting our criteria for donor milk will benefit from additional protein and micronutrient provision from increased fortification. It is also important to recognize that mother's milk may not be routinely tested for energy density, so the perceived calorie provision is based solely on calculated estimations. Additionally, research demonstrates that amount of nutritional antioxidants is significantly decreased in pasteurized donor milk in comparison to mother's own milk (contains only 18–53% the amount of maternal milk) (55). Despite fortification, research demonstrates slower growth on fortified, pasteurized donor human milk compared to raw fortified maternal milk or preterm infant formula (56–58). If this occurs, a transition to an appropriate preterm infant formula may be considered to optimize growth and promote optimal neurodevelopment.

If maternal or donor human milk is not utilized or sufficient to meet required feeding volumes, formula feedings can be initiated. These 24 calorie-per-ounce formulas can be provided at a range of 20–30 kcal/oz, yet the osmolalities of these formulas peak at 325 mOsm/kg water (59). The osmolality of a standard 24 kcal/oz formula (280–300 mOsm/kg water) (60) is fairly equivalent to unfortified MBM (290 mOsm/kg water) (45), so it is not beneficial to introduce at 20 calories/ounce and later

increase. Initiating at goal caloric densities will optimize early energy and protein intake while enteral feedings are not at goal, which becomes increasingly important when an infant is either receiving no supplemental PN or else limited peripheral PN with osmolarity limits. Very low birth weight infants exceeding 2.5 kg or 37 weeks gestational age should ideally continue receiving preterm infant formulas (even if at 22 calories/ounce) to optimize nutrients for bone mineralization and improved brain growth during a period of critical growth.

Enteral additives

The American Academy of Pediatrics recommends a daily dose of 400 international units of Vitamin D for all infants to prevent rickets (61). A previous study within a population of infants born <32 weeks demonstrated the average vitamin D level at birth to be low at 17.3 nanograms/millimoles, demonstrating improved levels with time and supplementation (62). Similarly, a recent study indicated that infants born <32 weeks demonstrated improved serum levels and bone mineralization at term corrected ages when having received vitamin D supplementation of 800 international units(IU)/day compared to 400 IU/day in addition to enteral feedings (63). Vitamin D₃ also remains available in concentrated form for infants receiving parenteral nutrition only. Iron is another additive for primarily human milk fed infants, however point of initiation remains variable. Many recommend starting at some point between 4–8 weeks of age, though there may be hematological and neurological benefits to earlier initiation at two weeks of age (64). The dosing range is 2–4 mg/kg/day for infants <1,500 grams (38,41). Probiotics are a controversial additive to the enteral feedings of very low birth weight infants, but a recent Cochrane review reported decreased severe NEC and all-cause mortality in infants <37 weeks gestational age or <2,500 grams (65,66). Some products are designed as a multi-strain probiotic supplement (i.e., containing *Lactobacillus* and *Bifidobacteria*), which are suggested as beneficial strains (66).

Growth

Goals

Providing adequate growth is a critical therapy for preterm infants. Weight loss from diuresis is normal in the first days of life, but should peak around day of life 4–6 with normal loss around 8–15% (67). While term infants may take two weeks to regain birth weight, this time period is may be quite long for the smallest preterm infants considering

a significant reduction in percentiles during this time. Growth guidelines vary depending on size, but consensus recommendations typically suggest an average gain of 15 grams/kg/day after initial loss (68). This however, likely poses as inadequate given high-end estimated intrauterine growth rates (38) and demonstration of frequent extrauterine growth restriction (1). For the smallest infants, a recommendation of at least 18 g/kg/day may be more optimal, as this has been associated with improved health outcomes and long-term neurodevelopment (3). Growth after achieving a weight of two kilograms typically ranges between 25–35 grams, which is the standard growth goals for a term-born infant <3 months of age (69). Inadequate or excessive growth should be avoided as preterm infants may be consequently susceptible to metabolic alterations in later life (70).

Poor growth

EUGR remains a high concern for preterm infants. As previously noted, roughly half of very low birth weight infants born in the United States are still discharged with weights plotting below the 10th% for age (1). After early initiation of PN and early achievement of appropriately fortified enteral feedings, the best way to minimize extrauterine growth restriction is by the early recognition of weight gain below goal levels. This includes infants who have significant delays in regaining birth weight and those who do not establish adequate, consistent weight gain after achieving full enteral feedings. Nutrition interventions can then be taken promptly to promote appropriate growth and prevent a further decline in growth percentiles.

The first way to optimize total calories/nutrition is to increase feeding volume. This is also feasible in chronic infants as a recent Cochrane review demonstrated no benefit to fluid restriction for infants with early bronchopulmonary dysplasia (71). If poor growth persists while on adequate volume, an increase in feeding caloric density may be warranted. If formula fed, preterm infant formulas are available at up to 30 calories/oz feedings. However, fortification beyond 24 calories/ounce for human milk becomes more difficult. This is because HMFs are not recommended to increase caloric density beyond 24 calories/ounce (39,48), the addition of powders is discouraged in the NICU setting to prevent cross-contamination (72), recommendations to keep osmolality of enteral feedings below 450 mOsm/kg of water (73), and the addition of other liquids dilutes the overall provision of mother's own milk. Units are therefore obligated to choose the best fortification strategies for the infants they

care for. Some may choose to add pre-measured preterm infant discharge formula powder to provide an additional 3–6 calories/ounce. One perceived benefit from this practice (compared to nutritional oils or concentrated formula) is that the formula powder will proportionally provide additional vitamins, minerals, and protein. In addition, it maintains a more standard ratio of carbohydrate-fat-protein. Another option is to add a nutritional oil to provide additional calories/ounce without affecting osmolality. Concentrated preterm infant formulas may be mixed at varying ratios with MBM to optimize nutrient provision, but this knowingly limits use of MBM.

Varying opinions exist regarding management of enteral feedings for infants with more severe established chronic lung disease. There remains a circular dilemma regarding management as these infants often experience an elevated resting energy expenditure due to a higher respiratory rate (19). As a result these infants benefit from enhanced nutrition (74), yet providing more daily calories (and carbohydrates) may be delayed due to clinical concern about this increasing respiratory rate. Past theories in adults suggest that higher fat, lower carbohydrate diets are advantageous for those with pulmonary diseases, as carbohydrates may increase carbon dioxide production (19). This strategy is not overwhelmingly applicable to neonatal populations. Firstly, it is important to recognize that the percentage of calories from dietary fat and carbohydrate differ at baseline between infants and adults. In example, references for human milk report roughly 52% of calories from fat and 42% of calories from carbohydrate (45). In comparison, the dietary reference intakes for adults suggest 20–35% of calories from fat and 45–65% of calories from carbohydrate (75). Secondly, there are no strongly conclusive recent studies correlating the positive effects of this low-carbohydrate, high fat diet strategy in preterm infants with bronchopulmonary dysplasia. In example, studies have demonstrated a lower measured respiratory quotient and less carbon dioxide production in infants with bronchopulmonary dysplasia receiving a lower carbohydrate/higher fat diet, yet there was no difference seen in respiratory rate (76,77). These studies were small and included only a short period of treatment (no more than one week) (76,77). Provision of total calories may be a more contributory factor influencing total carbon dioxide production, as overfeeding has consequences. Considering this, the best way to judge appropriate calorie provision in infants is by the appropriateness of weight gain while compared to linear growth. In contrary, infants receiving

inadequate nutrition will not only fail to meet adequate growth goals but subsequent potential for lung development will be impaired. Poor nutrition may also reduce level of lung function (74). Despite varying management strategies, it remains clearly evident that infants with chronic lung disease require close nutrition monitoring due to their intrinsically higher risk of growth failure (74), altered nutrient needs, and further growth faltering due to receiving dexamethasone therapy (78).

Excessive growth

While growth remains critical, it is important to promote appropriate growth for all anthropometric measurements, and not just an increase in adiposity. It is known that preterm infants have altered body compositions compared to their term-born counterparts (79). This is primarily due to a lower accumulation of lean body mass (79). Fat mass levels may also be higher in preterm infants compared to their term born counterparts (80-82). High weight gain and high level of fat mass may impose metabolic consequences, so the total provided calories should be limited if necessary. A decrease in feeding caloric density or a lower provision of total daily fluid will aid in modulating calorie intake. Research has demonstrated that gains in body mass index size from preterm birth until term corrected age confers neurological benefits, however increasing body mass size out of proportion to linear growth post-term does not confer additional benefits (83). Despite lower calorie provision if needed, it is still important to continue adequate protein, mineral, and vitamin provisions.

Discharge

There remain varying opinions regarding the most optimal discharge diet for preterm infants born <1,500 grams. This becomes most evident for infants who are receiving primarily MBM at discharge (84). Multiple recommendations are made for preterm infants having experienced extrauterine growth restriction or consequences of periods without adequate nutrition (i.e., osteopenia, etc.) (84), but no consensus recommendations for discharge feeding regimens have been concretely identified.

While adequate discharge feedings are essential and need to be further studied, a primary focus should be on providing adequate nutrition support and growth during hospitalization to prevent nutrient deficiencies by time of discharge. Hospitals have easy access to specialized fortification products, daily growth monitoring, and close nutrition management. This is much easier compared to outpatient management where resources may be limited and

monitoring is less frequent than an intensive care setting.

Infants discharging on formula often receive a preterm discharge formula, which has been associated with improved growth post discharge, particularly in linear growth and accretion of lean body mass (85). Discharge feedings for infants receiving primarily breast milk is more difficult. Units may opt to provide two feedings per day of this same preterm formula (with remaining feedings as breast milk) to optimize overall vitamin, mineral, and protein intake. Though this may not be unanimously practiced, a mixed diet of MBM and formula has been correlated to improved head circumference growth after NICU discharge, which has been further related to better neurodevelopmental scores (86). Mothers who wish to provide breast milk only may choose to provide several feedings per day of her pumped breast milk fortified with this same preterm formula powder, though this is a controversial practice secondary to the “sprinkles” dilemma (84). This does increase nutrient provision but far less compared to full formula feedings. MBM with HMF is a better nutritional option than formula powder post discharge, but this may impose financial or acquisition constraints for families.

Conclusions

Extensive review of available literature identifies best evidenced-based and clinically feasible enteral and parenteral nutrition support practices for infants born <1,500 grams to promote best outcomes. As with any recommendations suggested in this manuscript, medical care must be tailored to address the individual needs of each patient.

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Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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